Clinical trial results:
An Open-label, Randomized, Single-dose, 2-Period, 2-Treatment Crossover Study to Assess the Bioequivalence of Cinacalcet Capsule (Administered as Six of the 5-mg Cinacalcet Capsules) With 30-mg Commercial Cinacalcet Tablet in Healthy Adult Volunteers

Summary

EudraCT number	2017-002659-28
Trial protocol	Outside EU/EEA
Global end of trial date	28 December 2016

Results information

Result version number	v1 (current)
This version publication date	30 December 2017
First version publication date	30 December 2017

Trial information

Trial identification

Sponsor protocol code	20160428

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000078-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the bioequivalence, based on the area under the plasma drug concentration-time curve from time zero to infinity (AUCinf), area under the plasma drug concentration-time curve from time zero to a specific time point (AUC0-t), and the maximum observed concentration (Cmax), between the contents of six of the 5-mg cinacalcet capsules sprinkled over applesauce and a single 30-mg commercial formulation tablet of cinacalcet with applesauce in healthy adult volunteers.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable national and regional regulations/guidelines.
The protocol, proposed informed consent form, other written subject information, and any proposed advertising material were reviewed and approved by an institutional review board (IRB) before recruitment of subjects into the study and shipment of Amgen investigational product to the study site.
The investigator obtained written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product was administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	44
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a single site in the United States.

Pre-assignment

Screening details:

Healthy men and women who were 18 to 65 years of age (inclusive) at the time of randomization were eligible for participation in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Cinacalcet

Arm description:

Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.

Arm type	Experimental
Investigational medicinal product name	Cinacalcet Tablet
Investigational medicinal product code	
Other name	Sensipar® Mimpara®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce. The applesauce was consumed within 1 minute and dosing occurred within 1 minute of finishing the applesauce.

Investigational medicinal product name	Cinacalcet Capsules
Investigational medicinal product code	
Other name	Sensipar® Mimpara®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water.

Number of subjects in period 1	Cinacalcet
Started	44
Completed	43
Not completed	1
Decision by Sponsor	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.	

Reporting group values	Overall Study	Total	
Number of subjects	44	44	
Age Categorical Units: Subjects			
Adults (18-64 years)	44	44	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	38.1		
standard deviation	± 9.5	-	
Gender Categorical Units: Subjects			
Female	4	4	
Male	40	40	
Race Units: Subjects			
American Indian or Alaska Native	2	2	
Asian	2	2	
Black or African American	12	12	
Native Hawaiian or Other Pacific Islander	0	0	
White	27	27	
Other	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	19	19	
Not Hispanic or Latino	25	25	

End points

End points reporting groups

Reporting group title	Cinacalcet
Reporting group description:	
Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.	
Subject analysis set title	Cinacalcet 30 mg Capsule
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water	
Subject analysis set title	Cinacalcet 30 mg Tablet
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce.	

Primary: Maximum Observed Plasma Concentration (Cmax) of Cinacalcet

End point title	Maximum Observed Plasma Concentration (Cmax) of Cinacalcet
End point description:	
Cinacalcet in plasma samples was assessed using high performance liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS). Cinacalcet concentrations below the lower limit of quantitation (LLOQ, 0.100 ng/mL) were set to zero before data analysis.	
End point type	Primary
End point timeframe:	
Predose and up to 72 hours post-dose	

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: ng/mL				
arithmetic mean (standard deviation)	6.07 (± 3.62)	5.97 (± 3.38)		

Statistical analyses

Statistical analysis title	Statistical Evaluation of Cmax
Statistical analysis description:	
Cmax was natural log-transformed and analyzed using a mixed-effect analysis of variance (ANOVA) model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio. The number of subjects included in the analysis is 43, not 87.	
Comparison groups	Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Ratio of Capsule:Tablet
Point estimate	0.998
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.885
upper limit	1.126

Notes:

[1] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the Cmax, AUC0-t, and AUC0-inf geometric means were between 0.80 to 1.25.

Primary: Area Under the Plasma Drug Concentration-Time Curve From Time Zero to The Time of the Last Quantifiable Concentration (AUClast)

End point title	Area Under the Plasma Drug Concentration-Time Curve From Time Zero to The Time of the Last Quantifiable Concentration (AUClast)

End point description:

The area under the plasma drug concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast), estimated using the linear trapezoidal method (for assessment of the AUC0-t endpoint).

End point type	Primary

End point timeframe:

Predose to 72 hours post-dose

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	57.0 (± 34.0)	60.4 (± 39.1)		

Statistical analyses

Statistical analysis title	Statistical Evaluation of AUClast

Statistical analysis description:

AUClast was natural log-transformed and analyzed using a mixed-effect ANOVA model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and the corresponding 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio.
The number of subjects included in the analysis is 43, not 87.

Comparison groups	Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Ratio of Capsule:Tablet
Point estimate	0.945
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.861
upper limit	1.039

Notes:

[2] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the Cmax, AUC0-t, and AUC0-inf geometric means were between 0.80 to 1.25.

Primary: Area Under the Plasma Drug Concentration-Time Curve From Time Zero to Infinity (AUCinf)

End point title	Area Under the Plasma Drug Concentration-Time Curve From Time Zero to Infinity (AUCinf)

End point description:

End point type	Primary

End point timeframe:

Predose and up to 72 hours post-dose

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	43		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	63.5 (± 36.4)	66.1 (± 43.2)		

Statistical analyses

Statistical analysis title	Statistical Evaluation of AUCinf

Statistical analysis description:

AUCinf was natural log-transformed and analyzed using a mixed-effect ANOVA model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and the corresponding 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio.
The number of subjects included in the analysis is 43, not 85.

Comparison groups	Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Ratio of Capsule:Tablet
Point estimate	0.947

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.861
upper limit	1.042

Notes:

[3] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the Cmax, AUC0-t, and AUC0-inf geometric means were between 0.80 to 1.25.

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The severity of each adverse event was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria.

End point type	Secondary

End point timeframe:

From first dose of the investigational product in period 1 to day 14 (7 days in each treatment period).

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: participants				
Any adverse event (AE)	8	4		
AE Grade ≥ 2	1	0		
AE Grade ≥ 3	0	0		
AE Grade ≥ 4	0	0		
Serious adverse events (SAE)	0	0		
AE leading to discontinuation of cinacalcet	0	0		
Fatal adverse events	0	0		
Treatment-related adverse event	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration of Cinacalcet

End point title	Time to Maximum Observed Concentration of Cinacalcet

End point description:

End point type	Secondary

End point timeframe:

Predose to 72 hours post-dose

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: hours				
median (full range (min-max))	2.5 (1.0 to 6.0)	3.5 (1.0 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life of Cinacalcet (T1/2)

End point title	Half-life of Cinacalcet (T1/2)

End point description:

End point type	Secondary

End point timeframe:

Predose to 72 hours post-dose

End point values	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	43		
Units: hours				
arithmetic mean (standard deviation)	21.6 (± 9.58)	20.6 (± 9.19)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 14 Days (7 days in each treatment period)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Cinacalcet 30 mg Capsule
Reporting group description: Participants received a single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water.	
Reporting group title	Cinacalcet 30 mg Tablet
Reporting group description: Participants received a single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce.	
Reporting group title	All Subjects
Reporting group description: Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.	

Serious adverse events	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet	All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cinacalcet 30 mg Capsule	Cinacalcet 30 mg Tablet	All Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 44 (18.18%)	4 / 43 (9.30%)	11 / 44 (25.00%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Laceration			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Skin abrasion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Skin injury			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	3 / 44 (6.82%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	3	0	3
Somnolence			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	2 / 44 (4.55%)
occurrences (all)	2	0	2
Diarrhoea			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	2 / 44 (4.55%)
occurrences (all)	2	1	3

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	2 / 44 (4.55%)
occurrences (all)	1	1	2
Nausea			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	2 / 44 (4.55%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported